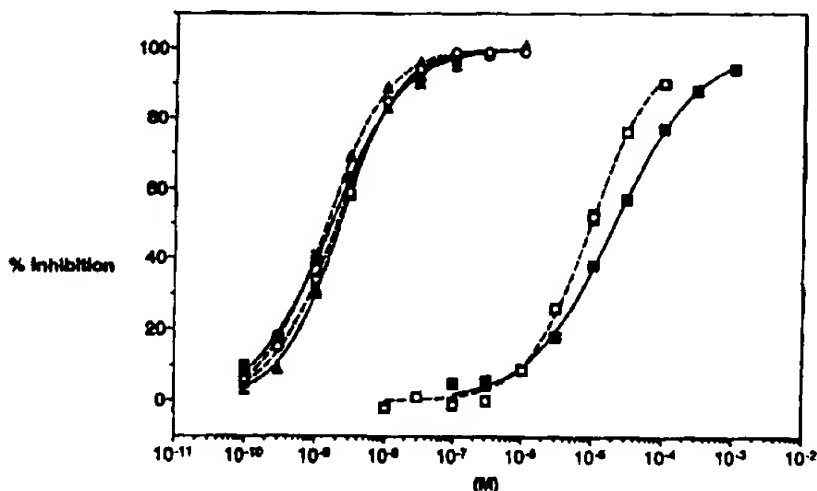




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/12, C07K 14/05, 16/28, G01N 33/68, C07F 9/30, C12N 15/11, A01K 67/027		A1	(11) International Publication Number: WO 97/46675
		(43) International Publication Date: 11 December 1997 (11.12.97)	
(21) International Application Number: PCT/EP97/01370		MICKEL, Stuart, John [GB/CH]; Heinisbodenweg 11, CH-4415 Lausen (CH).	
(22) International Filing Date: 19 March 1997 (19.03.97)		(74) Agent: ROTH, Bernhard, M.; Novartis AG, Patent- und Markenabteilung, Klybeckstrasse 141, CH-4002 Basel (CH).	
(30) Priority Data: 08/655,716 30 May 1996 (30.05.96) US 08/756,091 22 November 1996 (22.11.96) US		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(60) Parent Application or Grant (63) Related by Continuation US 08/756,091 (CIP) Filed on 22 November 1996 (22.11.96)		Published With international search report.	
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(54) Title: METABOTROPIC GABA[B] RECEPTORS, RECEPTOR-SPECIFIC LIGANDS AND THEIR USES



(57) Abstract.

The present invention provides purified GABA_B receptors and receptor proteins derived from rat and human sources, as well as nucleic acids which encode such proteins. The proteins and nucleic acids of the invention share significant homology with the GABA_B receptor and the DNA encoding it as specifically disclosed herein. The invention moreover provides methods for isolating other members of the GABA_B receptor family using DNA cloning technology and probes derived from the sequences provided herein, as well as novel members of the GABA_B receptor family isolated by such methods. Furthermore, the invention relates to the use of GABA_B receptors and receptor proteins and cells transformed with a gene encoding a GABA_B receptor protein in a method for identifying and characterising compounds which modulate the activity of the GABA_B receptor, such as GABA_B receptor agonists and antagonists, which may be useful as pharmacological agents for the treatment of disorders associated with the central and peripheral nervous systems.

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(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2620 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens

(vii) IMMEDIATE SOURCE:

- (B) CLONE: GABABR1a/b human

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION:1..2379

(ix) FEATURE:

- (A) NAME/KEY: mat_peptide
- (B) LOCATION:1..2379

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

GCA GTG TAC ATC GGG GCA CTG TTT CCC ATG AGC GGG GGC TGG CCA GGG
Ala Val Tyr Ile Gly Ala Leu Phe Pro Met Ser Gly Gly Trp Pro Gly
1 5 10 15

48

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GGC CAG GCC TGC CAG CCC GCG GTG GAG ATG GCG CTG GAG GAC GTG AAT	96
Gly Gln Ala Cys Gln Pro Ala Val Glu Met Ala Leu Glu Asp Val Asn	
20 25 30	
AGC CGC AGG GAC ATC CTG CCG GAC TAT GAG CTC AAG CTC ATC CAC CAC	144
Ser Arg Arg Asp Ile Leu Pro Asp Tyr Glu Leu Lys Leu Ile His His	
35 40 45	
GAC AGC AAG TGT GAT CCA GGC CAA GCC ACC AAG TAC CTA TAT GAG CTG	192
Asp Ser Lys Cys Asp Pro Gly Gln Ala Thr Lys Tyr Leu Tyr Glu Leu	
50 55 60	
CTC TAC AAC GAC CCT ATC AAG ATC ATC CTT ATG CCT GGC TGC AGC TCT	240
Leu Tyr Asn Asp Pro Ile Lys Ile Ile Leu Met Pro Gly Cys Ser Ser	
65 70 75 80	
GTC TCC ACG CTG GTG GCT GAG GCT GCT AGG ATG TGG AAC CTC ATT GTG	288
Val Ser Thr Leu Val Ala Glu Ala Ala Arg Met Trp Asn Leu Ile Val	
85 90 95	
CTT TCC TAT GGC TCC AGC TCA CCA GCC CTG TCA AAC CGG CAG CGT TTC	336
Leu Ser Tyr Gly Ser Ser Ser Pro Ala Leu Ser Asn Arg Gln Arg Phe	
100 105 110	
CCC ACT TTC TTC CGA ACG CAC CCA TCA GCC ACA CTC CAC AAC CCT ACC	384
Pro Thr Phe Phe Arg Thr His Pro Ser Ala Thr Leu His Asn Pro Thr	
115 120 125	
CGC GTG AAA CTC TTT GAA AAG TGG GGC TGG AAG AAG ATT GCT ACC ATC	432
Arg Val Lys Leu Phe Glu Lys Trp Gly Trp Lys Lys Ile Ala Thr Ile	
130 135 140	
CAG CAG ACC ACT GAG GTC TTC ACT TCG ACT CTG GAC GAC CTG GAG GAA	480
Gln Gln Thr Thr Glu Val Phe Thr Ser Thr Leu Asp Asp Leu Glu Glu	
145 150 155 160	

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CGA GTG AAG GAG GCT GGA ATT GAG ATT ACT TTC CGC CAG AGT TTC TTC	528
Arg Val Lys Glu Ala Gly Ile Glu Ile Thr Phe Arg Gln Ser Phe Phe	
165 170 175	
TCA GAT CCA GCT GTG CCC GTC AAA AAC CTG AAG CGC CAG GAT GCC CGA	576
Ser Asp Pro Ala Val Pro Val Lys Asn Leu Lys Arg Gln Asp Ala Arg	
180 185 190	
ATC ATC GTG GGA CTT TTC TAT GAG ACT GAA GCC CGG AAA GTT TTT TGT	624
Ile Ile Val Gly Leu Phe Tyr Glu Thr Glu Ala Arg Lys Val Phe Cys	
195 200 205	
GAG GTG TAC AAG GAG CGT CTC TTT GGG AAG AAG TAC GTC TGG TTC CTC	672
Glu Val Tyr Lys Glu Arg Leu Phe Gly Lys Lys Tyr Val Trp Phe Leu	
210 215 220	
ATT GGG TGG TAT GCT GAC AAT TGG TTC AAG ATC TAC GAC CCT TCT ATC	720
Ile Gly Trp Tyr Ala Asp Asn Trp Phe Lys Ile Tyr Asp Pro Ser Ile	
225 230 235 240	
AAC TGC ACA GTG GAT GAG ATG ACT GAG GCG GTG GAG GGC CAC ATC ACA	768
Asn Cys Thr Val Asp Glu Met Thr Glu Ala Val Glu Gly His Ile Thr	
245 250 255	
ACT GAG ATT GTC ATG CTG AAT CCT GCC AAT ACC CGC AGC ATT TCC AAC	816
Thr Glu Ile Val Met Leu Asn Pro Ala Asn Thr Arg Ser Ile Ser Asn	
260 265 270	
ATG ACA TCC CAG GAA TTT GTG GAG AAA CTA ACC AAG CGA CTG AAA AGA	864
Met Thr Ser Gln Glu Phe Val Glu Lys Leu Thr Lys Arg Leu Lys Arg	
275 280 285	
CAC CCT GAG GAG ACA GGA GGC TTC CAG GAG GCA CCG CTG GCC TAT GAT	912
His Pro Glu Glu Thr Gly Gly Phe Gln Glu Ala Pro Leu Ala Tyr Asp	
290 295 300	

GCC ATC TGG GCC TTG GCA CTG GCC CTG AAC AAG ACA TCT GGA GGA GGC	960
Ala Ile Trp Ala Leu Ala Leu Ala Leu Asn Lys Thr Ser Gly Gly Gly	
305 310 315 320	
GGC CGT TCT GGT GTG CGC CTG GAG GAC TTC AAC TAC AAC AAC CAG ACC	1008
Gly Arg Ser Gly Val Arg Leu Glu Asp Phe Asn Tyr Asn Asn Gln Thr	
325 330 335	
ATT ACC GAC CAA ATC TAC CGG GCA ATG AAC TCT TCG TCC TTT GAG GGT	1056
Ile Thr Asp Gln Ile Tyr Arg Ala Met Asn Ser Ser Ser Phe Glu Gly	
340 345 350	
GTC TCT GGC CAT GTG GTG TTT GAT GCC AGC GGC TCT CGG ATG GCA TGG	1104
Val Ser Gly His Val Val Phe Asp Ala Ser Gly Ser Arg Met Ala Trp	
355 360 365	
ACG CTT ATC GAG CAG CTT CAG GGT GGC AGC TAC AAG AAG ATT GGC TAC	1152
Thr Leu Ile Glu Gln Leu Gln Gly Gly Ser Tyr Lys Lys Ile Gly Tyr	
370 375 380	
TAT GAC AGC ACC AAG GAT GAT CTT TCC TGG TCC AAA ACA GAT AAA TGG	1200
Tyr Asp Ser Thr Lys Asp Asp Leu Ser Trp Ser Lys Thr Asp Lys Trp	
385 390 395 400	
ATT GGA GGG TCC CCC CCA GCT GAC CAG ACC CTG GTC ATC AAG ACA TTC	1248
Ile Gly Gly Ser Pro Pro Ala Asp Gln Thr Leu Val Ile Lys Thr Phe	
405 410 415	
CGC TTC CTG TCA CAG AAA CTC TTT ATC TCC GTC TCA GTT CTC TCC AGC	1296
Arg Phe Leu Ser Gln Lys Leu Phe Ile Ser Val Ser Val Leu Ser Ser	
420 425 430	
CTG GGC ATT GTC CTA GCT GTT GTC TGT CTG TCC TTT AAC ATC TAC AAC	1344
Leu Gly Ile Val Leu Ala Val Val Cys Leu Ser Phe Asn Ile Tyr Asn	
435 440 445	

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TCA CAT GTC CGT TAT ATC CAG AAC TCA CAG CCC AAC CTG AAC AAC CTG	1392
Ser His Val Arg Tyr Ile Gln Asn Ser Gln Pro Asn Leu Asn Asn Leu	
450 455 460	
ACT GCT GTG GGC TGC TCA CTG GCT TTA GCT GCT GTC TTC CCC CTG GGG	1440
Thr Ala Val Gly Cys Ser Leu Ala Leu Ala Ala Val Phe Pro Leu Gly	
465 470 475 480	
CTC GAT GGT TAC CAC ATT GGG AGG AAC CAG TTT CCT TTC GTC TGC CAG	1488
Leu Asp Gly Tyr His Ile Gly Arg Asn Gln Phe Pro Phe Val Cys Gln	
485 490 495	
GCC CGC CTC TGG CTC CTG GGC CTG GGC TTT AGT CTG GGC TAC GGT TCC	1536
Ala Arg Leu Trp Leu Leu Gly Leu Gly Phe Ser Leu Gly Tyr Gly Ser	
500 505 510	
ATG TTC ACC AAG ATT TGG TGG GTC CAC ACG GTC TTC ACA AAG AAG GAA	1584
Met Phe Thr Lys Ile Trp Trp Val His Thr Val Phe Thr Lys Lys Glu	
515 520 525	
GAA AAG AAG GAG TGG AGG AAG ACT CTG GAA CCC TGG AAG CTG TAT GCC	1632
Glu Lys Lys Glu Trp Arg Lys Thr Leu Glu Pro Trp Lys Leu Tyr Ala	
530 535 540	
ACA GTG GGC CTG CTG GTG GGC ATG GAT GTC CTC ACT CTC GCC ATC TGG	1680
Thr Val Gly Leu Leu Val Gly Met Asp Val Leu Thr Leu Ala Ile Trp	
545 550 555 560	
CAG ATC GTG GAC CCT CTG CAC CGG ACC ATT GAG ACA TTT GCC AAG GAG	1728
Gln Ile Val Asp Pro Leu His Arg Thr Ile Glu Thr Phe Ala Lys Glu	
565 570 575	
GAA CCT AAG GAA GAT ATT GAC GTC TCT ATT CTG CCC CAG CTG GAG CAT	1776
Glu Pro Lys Glu Asp Ile Asp Val Ser Ile Leu Pro Gln Leu Glu His	
580 585 590	

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TGC AGC TCC AGG AAG ATG AAT ACA TGG CTT GGC ATT TTC TAT GGT TAC	1824
Cys Ser Ser Arg Lys Met Asn Thr Trp Leu Gly Ile Phe Tyr Gly Tyr	
595 600 605	
AAG GGG CTG CTG CTG CTG CTG GGA ATC TTC CTT GCT TAT GAG ACC AAG	1872
Lys Gly Leu Leu Leu Leu Leu Gly Ile Phe Leu Ala Tyr Glu Thr Lys	
610 615 620	
AGT GTG TCC ACT GAG AAG ATC AAT GAT CAC CGG GCT GTG GGC ATG GCT	1920
Ser Val Ser Thr Glu Lys Ile Asn Asp His Arg Ala Val Gly Met Ala	
625 630 635 640	
ATC TAC AAT GTG GCA GTC CTG TGC CTC ATC ACT GCT CCT GTC ACC ATG	1968
Ile Tyr Asn Val Ala Val Leu Cys Leu Ile Thr Ala Pro Val Thr Met	
645 650 655	
ATT CTG TCC AGC CAG CAG GAT GCA GCC TTT GCC TTT GCC TCT CTT GCC	2016
Ile Leu Ser Ser Gln Gln Asp Ala Ala Phe Ala Phe Ala Ser Leu Ala	
660 665 670	
ATA GTT TTC TCC TCC TAT ATC ACT CTT GTT GTG CTC TTT GTG CCC AAG	2064
Ile Val Phe Ser Ser Tyr Ile Thr Leu Val Val Leu Phe Val Pro Lys	
675 680 685	
ATG CGC AGG CTG ATC ACC CGA GGG GAA TGG CAG TCG GAG GCG CAG GAC	2112
Met Arg Arg Leu Ile Thr Arg Gly Glu Trp Gln Ser Glu Ala Gln Asp	
690 695 700	
ACC ATG AAG ACA GGG TCA TCG ACC AAC AAC AAC GAG GAG GAG AAG TCC	2160
Thr Met Lys Thr Gly Ser Ser Thr Asn Asn Asn Glu Glu Glu Lys Ser	
705 710 715 720	
CGG CTG TTG GAG AAG GAG AAC CGT GAA CTG GAA AAG ATC ATT GCT GAG	2208
Arg Leu Leu Glu Lys Glu Asn Arg Glu Leu Glu Lys Ile Ile Ala Glu	
725 730 735	

- 62 -

AAA GAG GAG CGT GTC TCT GAA CTG CGC CAT CAA CTC CAG TCT CGG CAG	2256
Lys Glu Glu Arg Val Ser Glu Leu Arg His Gln Leu Gln Ser Arg Gln	
740 745 750	
CAG CTC CGC TCC CGG CGC CAC CCA CCG ACA CCC CCA GAA CCC TCT GGG	2304
Gln Leu Arg Ser Arg Arg His Pro Pro Thr Pro Pro Glu Pro Ser Gly	
755 760 765	
GGC CTG CCC AGG GGA CCC CCT GAG CCC CCC GAC CGG CTT AGC TGT GAT	2352
Gly Leu Pro Arg Gly Pro Pro Glu Pro Pro Asp Arg Leu Ser Cys Asp	
770 775 780	
GGG AGT CGA GTG CAT TTG CTT TAT AAG TGAGGGTAGG GTGAGGGAGG	2399
Gly Ser Arg Val His Leu Leu Tyr Lys	
785 790	
ACAGGCCAGT AGGGGGAGGG AAAGGGAGAG GGAAGGGCA GGGGACTCAG GAAGCAGGGG	2459
GTCCCCATCC CCAGCTGGGA AGAACATGCT ATCCAATCTC ATCTCTTGTA AATACATGTC	2519
CCCCTGTGAG TTCTGGGCTG ATTTGGGTCT CTCATACCTC TGGGAAACAG ACCTTTTTCT	2579
CTCTTACTGC TTCATGTAAT TTTGGAATTC CACCACACTG G	2620

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 793 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

.. (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Ala Val Tyr Ile Gly Ala Leu Phe Pro Met Ser Gly Gly Trp Pro Gly
1 5 10 15